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SEVERE TRAUMA – RISKS AND OUTCOMES

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Cover page: Civil war wound card 293, private Ludwig Kohn at
admission to Harewood U.S.A. Gen'l Hospital, August 15, 1865.
From *The medical and surgical history of the war of the rebellion (1861-65),*
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SEVERE TRAUMA – RISKS AND OUTCOMES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Rebecca, Julia and Hjalmar.

If we begin with certainties, we shall end in doubts;
if we begin with doubts, and are patient, we shall end in certainties.

Francis Bacon

If you can talk brilliantly about a problem,
it can create the consoling illusion that it has been mastered.

Stanley Kubrick

ABSTRACT

Trauma, "the neglected disease of modern society", is a global health concern of enormous proportions. Knowledge about factors associated with trauma occurrence, complications and outcome is highly valuable for the improvement of trauma care. This thesis, aiming at deeper knowledge regarding trauma occurrence and outcome, used regional and national registers in four epidemiological studies with different methodologies.

Prior to injury, trauma patients were treated for psychiatric disorders, substance abuse and somatic disorders to a greater extent than matched controls. Moreover, low income and low education, psychiatric disorders, substance abuse and somatic disorders were all independent risk factors for trauma after adjustment for confounders. These insights could facilitate implementation of injury prevention strategies.

Severely injured patients that use β-adrenergic receptor antagonists (β-blockers) at the time of trauma had an increased mortality compared to non-users, β-blockers could thus be seen as an indicator for increased risk of death. However, after adjustment for relevant confounders no increased risk, or benefit, of β-blockers *per se* was noted. The protective effect of β-blockade after severe trauma suggested by previous reports could not be supported. Prospective randomized trials are needed to elucidate a role, if any, for β-blockade in the trauma setting.

Acute kidney injury (AKI) affected one quarter of patients treated in the intensive care unit (ICU) following severe trauma. AKI was strongly associated with increased risk of death at 30 days and after one year. For those treated with renal replacement therapy the risk of chronic dialysis dependency after the intensive care period appears to be very low. Comorbidities such as diabetes mellitus as well as greater injury severity were strongly associated with post-injury AKI. Among preventable factors an association between resuscitation with hydroxyethyl starch (HES) and increased risk of AKI warrants caution. Administration of nephrotoxic substances should be avoided and targeted interventions may be provided to the patient at risk.

Finally, trauma patients had a sustained increase in mortality several years after the index trauma. External causes, including new trauma, were far more common causes of late death in injured patients than in the background population. These findings support the concept of trauma recidivism. Two subgroups of deceased individuals could be identified; younger patients with a high prevalence of psychiatric disorders and substance abuse dying from external causes including suicide, and an older subgroup with a burden of somatic comorbidities dying from cardiovascular disorders and neoplasms. These findings emphasize the need for improved follow-up strategies and secondary prevention.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I. **Socio-economic status and co-morbidity as risk factors for trauma**
Brattström O, Eriksson M, Larsson E, Oldner A
European Journal of Epidemiology 2015 Feb;30(2):151-7

II. **Pre-admission beta blockade in multiple trauma – A cohort study**
Eriksson M, von Oelreich E, Brattström O, Eriksson J, Larsson E, Oldner A
Manuscript

III. **Acute kidney injury following severe trauma: Risk factors and long-term outcome**
Eriksson M, Brattström O, Mårtensson J, Larsson E, Oldner A
Journal of Trauma and Acute Care Surgery 2015 Sep;79(3):407-12

IV. **Causes of excessive late death after trauma compared with a matched control cohort**
Eriksson M, Brattström O, Larsson E, Oldner A
British Journal of Surgery 2016 Sep;103(10):1282-9

CONTENTS

LIST OF ABBREVIATIONS

AIS	Abbreviated injury scale
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ARDS	Acute respiratory distress syndrome
β-blockers	β-adrenergic receptor antagonists
CA-AKI	Contrast associated acute kidney injury
CCI	Charlson comorbidity index
CI	Confidence interval
CRRT	Continuos renal replacement therapy
DALYs	Disability-adjusted life years
DAMPs	Damage-associated molecular patterns
HES	Hydroxyethyl starch
ICD	International classification of diseases
ICU	Intensive care unit
IQR	Interquartile range
ISS	Injury severity score
KDIGO	Kidney disease improving global outcomes
LISA	The Longitudinal Integration Database for Health Insurance and Labour Market Studies
MDRD	Modification of diet in renal disease
MI	Multiple imputations
MRR	Mortality rate ratio
NBHW	National board of health and welfare (*Sw. Socialstyrelsen*)
OR	Odds ratio
PAMPs	Pathogen-associated molecular patterns
RIFLE	Risk, injury, failure, loss, end-stage kidney disease
SAP	Systolic arterial blood pressure
SCB	Statistics Sweden (*Sw. Statistiska Centralbyrån*)
sCr	Serum creatinine
SIRS	Systemic inflammatory response syndrome

SweTrau	The Swedish trauma register
TBI	Traumatic brain injury
WHO	World health organization

1 INTRODUCTION

A severe traumatic injury is a devastating event for an individual and a challenge for health care systems and societies. It is undeniably a major global health concern that causes the death of millions every year, leaving many more injured. Moreover, in contrast to many other diseases, it predominantly affects younger individuals.

The development of dedicated trauma centers in many parts of the world has contributed to the decrease in trauma-related mortality noted in the last decades, but many challenges remain. It is of utmost importance that academic trauma centers are involved in all aspects of trauma care and research; organization, injury prevention, the pre-hospital phase, initial resuscitation and surgery, ICU treatment, in-hospital care, rehabilitation and long-term follow up. In this context, the majority of trauma studies have focused on initial resuscitation and surgery.

This thesis, based on four included studies, addresses several aspects of trauma with a focus on risk factors and short- and long-term mortality. The aim was to elucidate factors that contribute to the trauma patient's transition from health to illness, and eventually death. In study I, individual risk factors for becoming a trauma victim were studied with a special focus on socio-economy and comorbidity. Study II aimed to elucidate whether pre-traumatic treatment with β-blockers could be protective after severe trauma. In study III, the incidence of AKI and its relation to short and long-term mortality was examined among trauma patients treated in the ICU. In addition, risk factors for post-traumatic AKI were identified. In study IV, long-term mortality after trauma was analyzed and causes of excessive late death after trauma classified.

2 BACKGROUND

2.1 EPIDEMIOLOGY

Trauma is a leading cause of death and morbidity worldwide – the World Health Organization (WHO) estimate that more than five million individuals die each year as a result of injury. Injury thus accounts for almost 10 % of the world deaths and is the most common cause of death in individuals younger than 45 years of age in the Western world as well as in many of the developing countries. As an example, more than 200 000 individuals died from road traffic injuries in India 2013.[1] Globally, approximately a quarter of the fatalities are caused by traffic-related accidents and another quarter by homicide and other intentional injuries.[2,3] Among trauma-related deaths, WHO predicts that an increased proportion will be caused by road traffic injuries and falls in 2030 due to increased motorization and an aging population. This is supported by recent studies showing that patients admitted to trauma centers have become significantly older in the last decades.[4,5]

In Sweden, 4867 individuals died from injuries in 2016. Hence, external causes were the third and sixth most common cause of death in men and women respectively.[6] Although devastating, the millions of injuries with a fatal outcome only accounts for a small fraction of the injury burden to individuals and society. When comparing the impact on health using disability-adjusted life years (DALYs), the sum of years of life lost due to premature mortality and years lived with disability, injuries cause > 11 % of DALYs worldwide, placing it second only to cardiovascular diseases.[7]

2.2 TRAUMA SCORING SYSTEMS

There are several scoring systems in traumatology designed for classification of injuries, survival prediction and performance comparisons between centers. The Abbreviated Injury Scale (AIS) is an anatomical scoring system first published in 1971.[8] The seven-digit AIS-code specifies body region, specific structure, type and severity of injury. It is consensus-derived and classifies each injury severity according to its relative importance on a six-point scale, where six indicate an injury not compatible with survival. AIS is currently the system of choice for injury data collection and has become the basis for a number of other scales in use.

Injury Severity Score (ISS) is an anatomical description of injury that is designed to quantify the total load of anatomical injury across body regions. ISS is calculated by taking the sum of the squares of the AIS-codes for the most severe injury in each of the three most severely injured ISS body regions. The maximum score of ISS is 75. The body regions are divided into (1) head and neck, (2) face, (3) chest (thorax), (4) abdominal and pelvic contents, (5) extremities and bony pelvis and (6) external.[9] An ISS above 15 is generally defined as major trauma or severe injury.[10]

2.3 TRENDS IN TRAUMA CARE – ARE WE DOING BETTER?

Several interventions have been shown to decrease mortality and improve outcome in the trauma setting. For example, the centralization of trauma care into centers with around-the-clock availability of experienced and dedicated physicians has been shown to increase survival.[11] Another aspect is the concept of hemostatic resuscitation and avoidance of traumatic coagulopathy. Although the exact ratio and timing of included components and monitoring of effects remain to be confirmed, the concept is probably beneficial in terms of reduced bleeding and increased survival.[12-15] Moreover, the severely injured trauma patient is likely to benefit from general measures that have been shown to decrease mortality in the ICU such as lung-protective ventilation in severe Acute Respiratory Distress Syndrome (ARDS).[16]

Treatments that are beneficial for the patient should be introduced, but of equal importance is the avoidance of harmful interventions. In the ICU for example, tight glucose control, administration of HES to septic patients and ventilation with large tidal volumes have all been shown to be harmful and should be avoided.[16-18]

Short-term mortality among patients reaching hospital alive after trauma seems to decrease as an effect of these and other interventions.[4,19,20] This trend, however, is counteracted by the significant increase in age of trauma patients in the last decades.[4,20,21]

2.4 THE TRAUMA PATIENT'S JOURNEY – FROM HEALTH TO ILLNESS AND BACK AGAIN

2.4.1 Risk factors for trauma occurrence

Globally, males are twice as likely as females to die from injury and this difference is most apparent in individuals between 15-44 years of age.[22] Men are also more prone to experience non-fatal injuries. Among patients admitted to the trauma unit and included in the Trauma Register at the Karolinska University Hospital, Stockholm more than two thirds are male.[23]

Previous studies indicate that there is an association between residency in a region with lower socioeconomic status and an increased risk of traumatic events as well as death due to trauma.[24-26] In addition, socioeconomic positions seem to increase the risk of experiencing trauma at an individual level.[25,27,28] The reason for the variation in injury risk is probably multifactorial but not fully elucidated. Moreover, many studies on the association between socioeconomic factors and the risk of trauma have focused on specific mechanisms of injury such as road traffic incidents or self-harm.[29]

Clinical experience and previous studies indicate a close connection between alcohol and trauma. Alcohol intoxicated individuals have a significantly increased risk of injury, with additional risk with higher alcohol intake in a dose-response pattern.[30,31] Excessive long-term alcohol consumption increases the risk of trauma as well, with a similar dose-response effect.[31] Efforts have been made to calculate the alcohol-attributable effect on trauma incidence. In a recent study by Cherpitel *et al.*, including > 14000 patients from 18 countries

almost 17 % of all trauma cases in the emergency department were attributed to alcohol.[32] In addition, previous studies suggest that a significant proportion of trauma patients are suffering from psychiatric disorders and substance abuse.[33] Drug users have a known increased mortality compared to non-users, in part explained by traumatic deaths.[34] Although findings from one specific region or specific centers might have reduced generalizability, a high prevalence of positive drug-tests has been noted in deceased trauma patients.[35] Moreover, there is a high and potentially increasing incidence of use and misuse of prescribed narcotics and benzodiazepines among victims of trauma.[36]

The presence of somatic comorbidities increases the risk of fatal outcomes and complications after trauma but to what extent they contribute to the risk of trauma has not been fully elucidated.[37-39] The strength of association between the presence of somatic comorbidities and outcome after trauma varies depending on definitions, case-mix, injury severity, age and follow-up.[23]

In summary, many studies have investigated the association between specific socioeconomic positions or comorbidities and specific subgroups of injuries. Socioeconomic variables and comorbidities, however, are likely to be related and have not been analyzed together in previous studies in the trauma setting.

2.4.2 The post-resuscitation phase – focus on organ failure

Mortality in trauma research has since the influential work in the late seventies by Baker and Trunkey been classified as trimodal, based on the time elapsed from incident to death.[40,41] Immediate deaths on scene has mainly been attributed to unsurvivable injuries to the central nervous system, heart or large vessels. The majority of injury-related deaths still occur on scene or before arrival to the hospital.[42]

Severe brain injuries and exsanguination are also the most common causes of early death within the first 48 hours in-hospital.[43] The concept of a third "peak" of deaths within days to weeks after hospital admission, as described by Trunkey, does not seem to be accurate in modern trauma care where a continuous decline is a more accurate description.[44-46] A significant proportion of post-traumatic deaths still occur in this phase where the most important causes of death are sepsis and multiple organ failure (MOF) in addition to traumatic brain injuries.[43,44]

Individuals surviving the initial injury and the resuscitation phase including surgery are at high risk of later complications potentially altering the clinical course. MOF, ARDS, sepsis and AKI are known contributors to increased mortality and morbidity among the severely injured. Direct, traumatic lesions to the lungs, intestines, kidneys and other involved organs increases the risk of these conditions but the development of MOF is complex and not fully understood. The reaction to severe trauma seems to be similar to other causes of the Systemic Inflammatory Response Syndrome (SIRS), such as sepsis, with overwhelming activation of pro- and anti-inflammatory pathways and the coagulation system, glycocalyx degradation and endothelial damage and disturbed microcirculation.[47-49]

The innate immune system can be activated by exogenous compounds from invading microorganisms (pathogen associated molecular patterns, PAMPs), or by endogenous molecules like S100-proteins and mitochondrial DNA (damage-associated molecular patterns, DAMPs) in the absence of infection. An excessive, systemic activation of the immune system and an imbalanced production of inflammatory factors are believed to cause organ dysfunction.[47,48,50] Factors shown to be associated with subsequent MOF are age, ISS and other markers of injury severity, massive transfusion and coagulopathy, severe head injury and male gender.[51-54] The risk of death increases with increasing number of failing organs.[55] Improvements in the initial phases of trauma care may present more severely injured patients to the ICU, individuals that previously would not have survived (Figure 1). This, in combination with the increased age of admitted trauma patient might explain the increased incidence of MOF noted in some studies.[53]

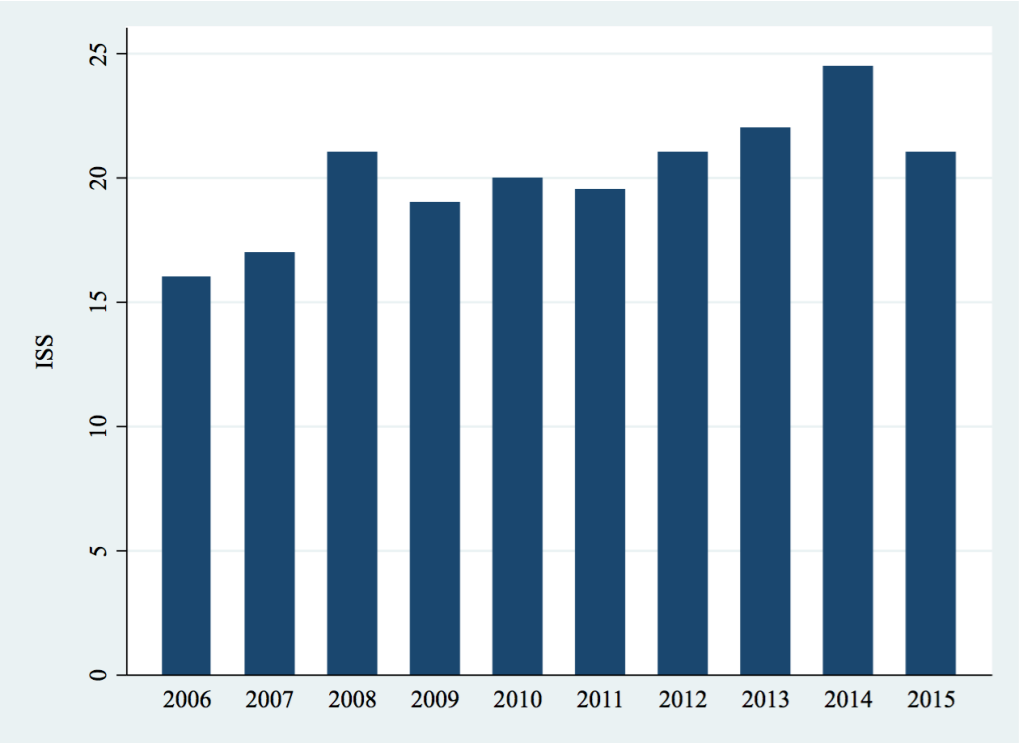


Figure 1. Median Injury Severity Score (ISS) per year for patients admitted to the Central-ICU or the Neuro-ICU at Karolinska University Hospital.

2.4.2.1 β-blockade – protective?

An established prophylaxis or targeted treatment for post-traumatic organ failure is lacking. In the last years, a proposed link between severe trauma and endothelial injury with subsequent coagulopathy, mediated through sympatho-adrenal hyperactivation has been presented (Figure 2).[56] An increase in plasma catecholamines has been associated with markers of endothelial and glycocalyx damage, as well as signs of hypocoagulability.[57] In this context, the administration of β-blockers to trauma patients seems to be a logic therapeutic

possibility to improve organ function and survival. Animal data indicate that administration of β-blockers might have anti-fibrinolytic and endothelial protective effects mediated via reduced sympathetic hyperactivity, thus suggesting a causal link.[58] The positive results from β-blocker administration in sepsis, a condition with many similarities to severe trauma, further strengthen this hypothesis.[59,60]

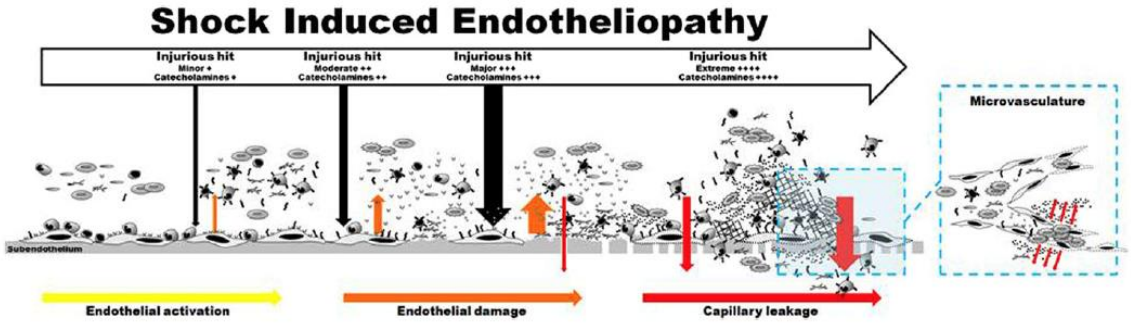


Figure 2. Shock-induced endotheliopathy (SHINE). Schematic illustration of the changes in the vascular compartment with increasing disease severity and increasing sympatho-adrenal activation. From Johansson *et al.*, no changes made.[56] Reprinted under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Since traumatic coagulopathy occurs immediately, on the scene of accident, it is likely that endothelial damage and exposure of sub-endothelial structures is an early process as well.[57,61] Given that, having circulating levels of β-blockers in plasma already at the time of trauma might be protective. A few studies on the association between pre-traumatic β-blockade treatment and mortality have been presented with diverging results. In multiple trauma, studies have shown no difference or even increased mortality with β-blocker use whereas a protective effect has been noted in traumatic brain injury (TBI).[62-66]

There are several plausible mechanisms for the absence of a protective effect in previous studies. First, a blunted hemodynamic response to injury with subsequent hypotension induced by β-blockers could have detrimental effects as previously shown.[67] Secondly, imbalances in comorbidities at baseline might be difficult to adjust for in retrospective studies and the presence of significant comorbidities may have a profound effect on post-traumatic survival.[5,37,38,63]

2.4.2.2 Acute kidney injury

AKI is common among intensive care patients in general and among patients admitted with severe trauma, and closely associated with increased mortality.[68-72] Studies suggest that AKI is a stronger predictor of fatal outcomes, such as multiple organ failure and death, among trauma patients than failure in other organ systems.[73] The previous absence of a uniformly accepted definition of AKI has hampered research in the field of post-traumatic AKI but consensus definitions have been introduced in the last decades. In 2004 the Acute Dialysis

Quality Initiative introduced the first evidence-based consensus definition, the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) classification based on a relative increase in serum creatinine (sCr) compared to baseline or a decrease in urine output.[74] The RIFLE criteria were modified into the Acute Kidney Injury Network (AKIN) classification in 2007 with the aim of improving sensitivity.[75]

In 2013 a new definition merging the RIFLE and AKIN criteria was proposed by the Kidney Disease Improving Global Outcomes (KDIGO) group (Table 1).[76] Previous studies comparing the different criteria have yielded conflicting results but the KDIGO criteria might be a more robust predictor of outcome.[77,78]

Table 1. Staging of AKI in adults according to KDIGO.

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline*	< 0.5 ml/kg/h for 6-12 hours
	OR	
	≥ 0.3 mg/dl (≥ 26.5 μmol/l) increase**	
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline	< 0.3 ml/kg/h for ≥ 24 hours
	OR	**OR**
	Increase to ≥ 4.0 mg/dl (≥ 354 μmol/l)	Anuria for ≥ 12 hours
	OR	
	Initiation of renal replacement therapy	

* *Known or presumed to have occurred within the prior 7 days.*
** *Within 48 hours.*

AKI, defined by RIFLE or AKIN, following severe trauma has an incidence of 10-30 % varying with definitions and case mix.[70,79,80] The risk of post-traumatic AKI is affected by patient factors, trauma-related factors and treatment factors. Regarding pre-traumatic characteristics, increased age is consistently associated with an increased risk of AKI. A higher prevalence of AKI is also noted in the presence of comorbidities such as obesity, diabetes mellitus and diseases of the cardiovascular system.[70-72]

Increased injury severity, defined either by ISS or physiological derangement such as elevated lactate or base deficiency, is closely linked to subsequent AKI.[72,79-81] Although uncommon, direct lesions to the kidneys or the urinary tract can lead to reduced kidney function following injury.[82] Much focus in trauma research in the last decade has been towards resuscitation strategies including reduced amounts of crystalloids and the administration of high ratios of fresh frozen plasma and platelets to red blood cells in the

bleeding patient. The aim of this damage control resuscitation is to prevent the development of acute traumatic coagulopathy and to optimize oxygen delivery capacity. This approach seems to reduce the number of deaths due to exsanguination and might improve overall survival.[14,83] In contrast, blood product administration has been associated with increased risk of post-traumatic AKI.[71,79]

There has been much concern regarding the administration of artificial colloids to critically ill patients and an increased risk of AKI, with particular focus on HES that has been convincingly associated with AKI among patients with sepsis.[18,84,85] In the trauma setting, older compositions with larger starch-molecules and higher-molar substitutions such as HES 450/0.7 have been associated with AKI in retrospective studies.[86,87] On the contrary, a single-center RCT found that administration of HES 130/0.4 was associated with a lower incidence of AKI among patients with penetrating trauma compared to 0.9 % saline.[88]

2.4.3 Long-term outcomes

Trauma outcome has traditionally been measured in a short-term perspective as in-hospital or 30-day mortality, a recommended endpoint in trauma registers and research in Europe.[89] However, several studies on long-term outcome indicate that short-term mortality poorly reflects the overall mortality attributed to trauma. When compared to the background population, or a matched comparison group, trauma patients seem to have a significantly increased mortality in several years following trauma.[90-94] This increase in long-term mortality may counterbalance the improvements in short-term outcome, i.e. in-hospital mortality decreases but overall mortality remains unchanged.[93]

Although the increased late mortality in this group of patients is significant and seems consistent across the western world, few studies have investigated the causes of late death. In a study from Baltimore the most common causes of late death were external causes, such as new trauma or intoxication, being responsible for almost 40 % of post-discharge deaths.[95] Not surprisingly, diseases of the circulatory system were the most common somatic cause of death. These results must be generalized with caution due to the extremely high proportion of intentional violence (56 %) and penetrating injury (43 %) in the study cohort. Another US study reported that one third of post-discharge deaths were attributed to trauma.[96] In the only European data published, external causes and diseases of the circulatory system were the most common causes of late death following trauma.[92] Thus, late death after trauma appears to be a substantial but underestimated problem.

3 AIMS OF THE THESIS

To examine the influence of socioeconomic factors and comorbidity on the risk of becoming a trauma victim.

To investigate whether pre-traumatic β-blocker therapy could be protective after severe, multiple trauma.

To analyze the incidence of post-traumatic AKI and the long-term effects regarding survival and end-stage renal disease among trauma patients treated in the ICU.

To identify patient-related and modifiable factors associated with post-traumatic AKI.

To evaluate increased long-term mortality among trauma victims and identify causes of excess late mortality.

4 MATERIALS AND METHODS

4.1 NATIONAL REGISTERS

The unique, 12-digit personal identity number provided to all Swedish citizens allows linkage of patient data to national and regional registers.[97]

4.1.1 The Register of Total Population

Statistics Sweden (SCB) is responsible for the Register of Total Population since its establishment in 1968. The register holds information on national registration, marital status, citizenship etcetera and is subsequently providing information to other registers.[98]

4.1.2 The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA)

The LISA-register is linked to several other national registers and holds information on individuals of age 16 or older. It is run by SCB and provides individual information on employment, income and highest achieved education in addition to other socio-economic variables.[99] It has been annually updated since 1990.

4.1.3 The National Patient Register

Starting out in a small-scale in 1964, and subsequently expanded, The National Patient Register is managed by the Swedish National Board of Health and Welfare (NBHW). It contains information on all in-patient care episodes in psychiatric care since 1973 and in somatic care since 1987. Specialized outpatient care, i.e. not primary care, is included from 2001. The initial coverage for outpatient care was below 75 % regarding the main diagnose in the first years but has improved over time and is now considered to be > 95 %.[100,101]

Each care episode is registered with data on personal identity number, hospital or clinic and admission and discharge dates. Diagnosis, of which one is principal, is listed according to International Classification of Diseases (ICD) coding. ICD version 10 has been used in Sweden since 1997.

4.1.4 The Cause of Death Register

The Cause of Death Register, managed by NBHW, contains data from 1961 and onwards. All deceased Swedish citizens are included, regardless of place of death.[102] In addition, from 2012 all deaths occurring in Sweden are included regardless of national registration for the individual. The physician that determines death is responsible that a cause of death report is submitted to NBHW. According to WHO standards the cause of death is registered according to ICD-10 codes. The immediate cause of death, i.e. the final disease or condition that resulted in death is registered as primary cause of death. The conditions that lead up to the

primary cause of death is subsequently listed, with the underlying cause of death defined by WHO as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury".[103]

The coverage is considered excellent with < 1 % loss of death certificates. Misclassifications of the underlying cause of death have been estimated to approximately 20 % overall but vary with age and diagnose groups. It is considered to be lower among younger individuals and in patients with violent causes of death, malignancies and ischemic heart disease.[104]

4.1.5 The Prescribed Drug Register

The Prescribed Drug Register contains information on all prescribed drugs dispensed at pharmacies in Sweden. It is managed by the NBHW and the addition of personal identity numbers on July 1st 2005 made linkage to other registers possible from that date. It is considered to have 100 % coverage regarding dispensed drugs. Medications administered in hospitals and some nursing homes are not included, there are also some missing data on drugs administered in day-care such as biologic drugs against rheumatoid arthritis and cancer treatments.[105-107]

4.2 REGIONAL REGISTERS

The relationship between regional registers are presented in Figure 3.

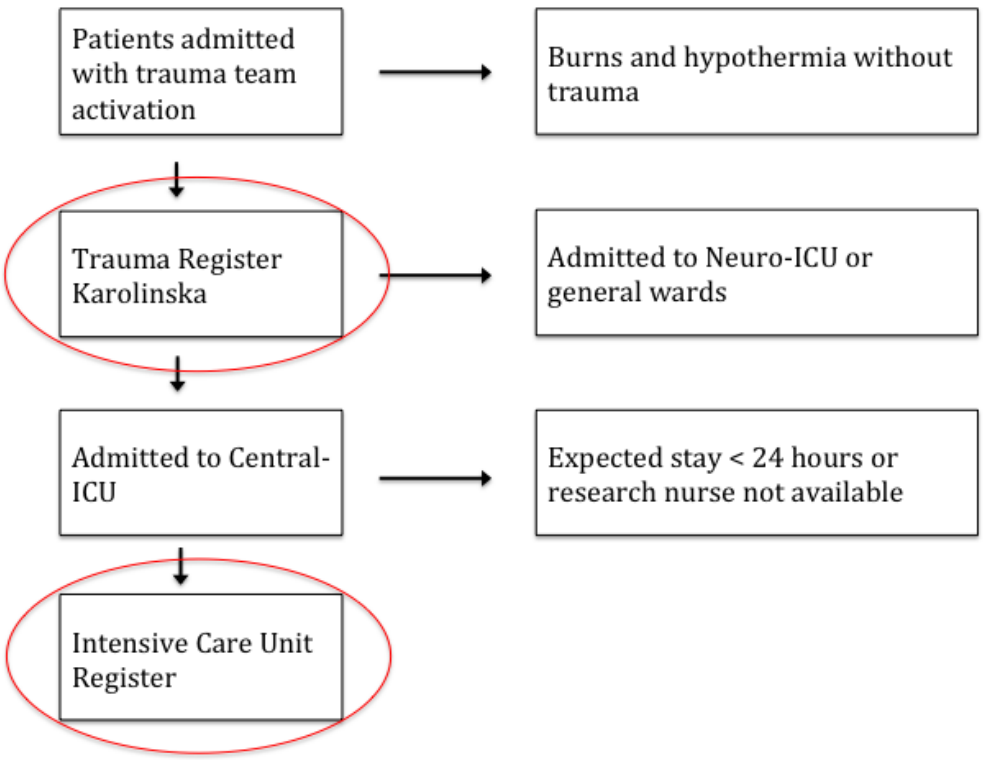


Figure 3. Flow chart of the relation between regional trauma registers.

4.2.1 Trauma Register Karolinska

All patients admitted with full trauma team activation have been included in the Trauma Register of the Karolinska University Hospital since 2005. It holds information on pre-hospital as well as in-hospital care, admission time, trauma mechanism, physiological derangement and outcome variables. Patients admitted without full trauma team activation but retrospectively found to have injuries with an ISS of > 9 are also included. Patients with severe burns or hypothermia without other traumatic injuries, chronic subdural hematomas or isolated fractures of the extremities are not included. The Trauma Register Karolinska reports data to the Swedish Trauma Register (SweTrau) from 2013 and data are registered according to the Utstein Template from the same year.[89]

4.2.2 The Intensive Care Unit Register

From February 2007, trauma patients age 15 or older with an expected ICU stay of more then 24 hours admitted to the Central ICU at the Karolinska University Hospital are included in a database. Research nurses collect detailed information on organ failure, specific treatment and outcome variables daily. Data are verified twice to ensure quality and pre-hospital and baseline data are added retrospectively from the Trauma Register Karolinska. Data collection continues until discharge from the ICU or death.

4.3 DEFINITIONS

Education was categorized from the highest achieved level in the year of trauma as low, medium or high corresponding to ≤ 9, 10 - 12 or > 12 years of schooling respectively. Thus, high education equals university level in the Swedish school system. Income was classified as low, medium or high corresponding to < 50 %, 50 - 200 % or > 200 % of the median income in Sweden the year preceding trauma. Comorbidities were extracted from the Patient Register (Paper I, II and IV) and from patient charts (Paper III). Somatic comorbidity was defined as the presence of any of the somatic diagnosis included in the Charlson Comorbidity Index (CCI) up to eight years prior to trauma (Paper I and IV) and analyzed individually as specified in Paper II. In Paper III diabetes mellitus was extracted from the CCI and analyzed as a separate entity. The CCI was coded from ICD-10 as previously described.[108,109] Psychiatric comorbidity and substance abuse were defined as the presence of any of ICD-10 codes F20-F99 and F10-F19 respectively.

4.4 STATISTICS

Data are in general presented as count (%) or median with interquartile range (IQR) as depicted in tables. Continuous variables were considered non-normally distributed and compared with Mann-Whitney U test or Kruskal-Wallis test as appropriate. Proportions were compared with χ^2-test or Fisher's exact test depending on sample size and frequency distribution. Differences in survival in Paper II-IV were compared with log rank test. Differences in survival over specific time intervals in Paper IV were calculated from deaths per person-time in each group, as mortality rate ratios (MRR) with corresponding 95 %

confidence intervals (CI). Predictors of trauma risk in Paper I were analyzed with logistic regression analysis conditional on matched group. Adjustment for confounders in Paper II and risk factor analyses in Paper III was performed with multivariable logistic regression. Results from regression analyses are presented as odds ratios (OR) with 95 % CI. Data was analyzed as complete cases (Paper I and III) and as complete cases and with multiple imputations (MI) (Paper II). Hosmer-Lemeshow test was used to analyze model performances. $P < 0.050$ was considered statistically significant, all tests two-tailed. IBM SPSS Statistics version 21.0 and 22.0 (IBM, Armonk, NY, USA), Stata/SE 14.2 (StataCorp, College Station, TX, USA) and GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA) were used for statistical analyses.

4.5 STUDY DESIGN AND OUTCOME MEASURES

Study design and outcome measures are summarized in Table 2.

Table 2. Study design and outcome measures.

Study	**I**	**II**	**III**	**IV**
Design	Case-control	Cohort study	Cohort study	Matched cohort study
Study population	Prospectively collected trauma cohort 2005-2010	Prospectively collected trauma cohort 2005-2015	ICU-treated trauma patients Feb. 2007-Sept. 2012	Prospectively collected trauma cohort 2005-2010
Sample size	Cases 7382 Controls 36760	1376	413	Patients 7382 Controls 36759
Register used	Trauma Register Patient Register LISA Register of Total Pop.	Trauma Register Patient Register LISA Register of Total Pop. Cause of Death Register Prescribed Drug Register	Trauma Register Intensive Care Unit Register	Trauma Register Patient Register Register of Total Pop. Cause of Death Register
Follow up	-	30 days	1 year	Min. 1 year, mean 3.5 years
Outcome measures	Event: Trauma Exposure: socioeconomic factors, comorbidity	Association between pre-traumatic β-blockade and mortality	Incidence of AKI, risk factors for AKI, 30-day and one year mortality	MRR, causes of late death beyond 30 days

4.5.1 Study I

In a case-control study, injured patients from the Trauma Register Karolinska between 2005-2010 (cases) were matched by age, gender and municipality in a 1:5-ratio to uninjured individuals from the Register of Total Population (controls). Baseline data on income and education were extracted from LISA and data on comorbidities from the Patient Register. The relative importance of socio-economic status and comorbidities on trauma risk was explored with regression analysis. The time-dependency of included comorbidities was evaluated by analyzing a more recent (< 6 months prior to trauma) diagnosis separately.

4.5.2 Study II

Patients from the Trauma Register Karolinska 2006-2015, age > 50 and ISS > 15 were extracted and included in a cohort study. Patients not expected to survive regardless of treatment, defined as ISS = 75, were excluded. Patients were linked to LISA and the Patient Register, thus providing baseline data on socio-economy and comorbidity. Individuals were also linked to the Prescribed Drug Register to define β-blocker use at the time of trauma. The association between pre-traumatic β-blocker use and 30-day mortality was explored using multivariable logistic regression with adjustment for important baseline imbalances, comorbidities and trauma-related factors.

4.5.3 Study III

Patients included in the ICU Register from February 2007 - September 2012 were analyzed in a cohort study. The outcome measure was AKI according to the KDIGO classification occurring day 2 - 7 after admittance.[76] Individuals that died before day two and those with a known chronic kidney disease were excluded. The patients were followed for one year with respect to survival and end-stage kidney disease. Logistic regression analysis was used to identify factors associated with AKI occurrence.

4.5.4 Study IV

All injured patients from the Trauma Register Karolinska 2005-2010 were matched by age, gender and municipality in a 1:5-ratio to uninjured controls from the Register of Total Population. Socio-economic variables and comorbidity were assessed by linkage to LISA and the Patient Register, and cause of death by linkage to the Cause of Death Register. The cause of death was defined as the immediate cause of death noted in the cause of death certificate. In a matched cohort study long-term mortality was compared with MRR for specific time-periods between injured and uninjured individuals up to three years after the index trauma. Causes of death were compared within the trauma cohort, stratified by time to death, and between the trauma cohort and the control group.

5 RESULTS

5.1 STUDY I

7382 trauma patients (cases) and 36760 controls were included. Compared to the controls, fewer trauma patients had achieved university level of education or had high income. All included comorbidities were more common among trauma patients. These differences were unchanged when restricting the analysis to the most severely injured group (ISS > 15). The distribution of injury mechanisms differed between categories of education and income. Assault was three times more common among those with a low level of education and almost four times more common among those with low income, compared to those with the highest education and income.

In the conditional logistic regression analysis both level of education and income, and all included comorbidities (somatic, psychiatric and drug abuse) were significantly associated with the risk of trauma. This association was unchanged when analyzing the most severely injured separately, except from somatic comorbidity no longer being a risk factor (Table 3).

Table 3. Conditional logistic regression analysis of level of education, income and comorbidity as risk factors for trauma. Odds ratios with 95 % confidence interval. Analysis of all patients and stratified for injury severity (ISS > 15).

	Odds Ratio (95 % CI)		**Odds Ratio (95 % CI)**	
	All		ISS >15	
	unadjusted	adjusted	unadjusted	adjusted
Level of education				
Low	1.8 (1.7-1.9)	1.5 (1.4-1.6)	1.7 (1.5-1.9)	1.4 (1.2-1.6)
Medium	1.5 (1.4-1.5)	1.3 (1.3-1.4)	1.5 (1.3-1.7)	1.3 (1.1-1.5)
High	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Income				
Low	1.8 (1.6-2.0)	1.2 (1.1-1.3)	2.0 (1.6-2.6)	1.3 (1.1-1.7)
Medium	1.5 (1.3-1.6)	1.2 (1.1-1.4)	1.7 (1.3-2.2)	1.4 (1.1-1.8)
High	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Comorbidity				
Psychiatric diagnosis	2.1 (2.0-2.3)	1.5 (1.4-1.6)	2.1 (1.8-2.4)	1.4 (1.2-1.6)
Substance abuse diagnosis	3.3 (3.1-3.5)	2.6 (2.4-2.8)	3.9 (3.4-4.4)	3.4 (3.0-4.0)
Somatic diagnosis	1.3 (1.2-1.3)	1.1 (1.1-1.2)	1.2 (1.1-1.3)	1.0 (0.9-1.1)

The analysis for time dependency showed that a recent diagnosis, i.e. within 6 months, of substance abuse or somatic disorders increased the risk of trauma significantly (Figure 4).

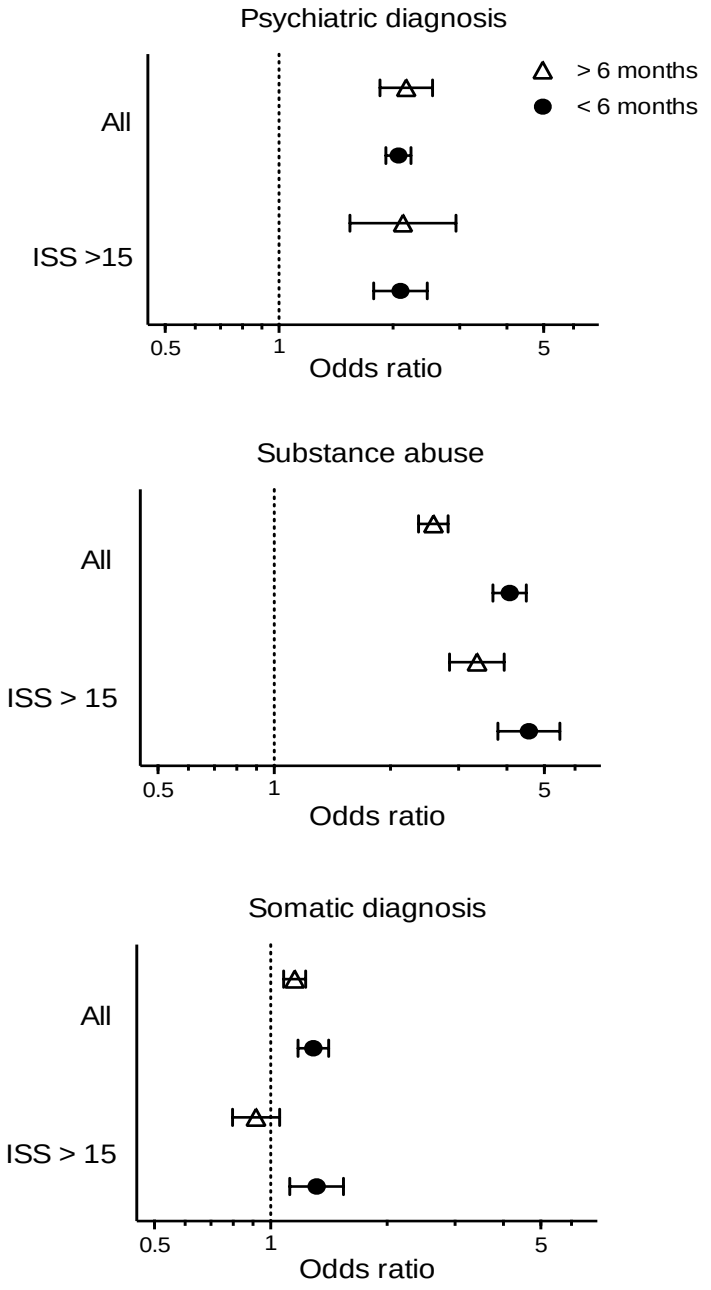


Figure 4. Impact of treatment for psychiatric comorbidity, substance abuse or somatic disorder within six months on the risk of trauma. The figure displays how the adjusted odds ratio (95% confidence interval) for trauma is affected by having the most recent treatment within six months (closed circles) as compared with before six months (open triangles) at the time of injury for all and severely injured (ISS > 15) patients respectively. All analyzes adjusted for socio-economic status.

5.2 STUDY II

1376 severely injured patients, age > 50 were included in the final analysis. Of these, 338 (24.6 %) received β-blockers at the time of trauma. There was no significant difference in injury severity between β-blocker users and non-users. The first recorded blood pressure was similar and patients from both groups expressed shock on arrival and were treated in the ICU to the same extent (Table 4).

Table 4. General characteristics and clinical outcome in the study cohort stratified by β-blocker therapy.

	β-blocker (-)	**β-blocker (+)**	**p**
Count (%)	1038 (75.4)	338 (24.6)	
Age, median (IQR)	63.5 (56-73)	71.5 (63-82)	< 0.001
Male, count (%)	733 (70.6)	223 (66.0)	0.108
Education level, count (%)			
Low	240 (25.1)	88 (30.6)	0.175
Medium	444 (46.3)	125 (43.4)	
High	274 (28.6)	75 (26.0)	
CCI, median (IQR)	0 (0-1)	1 (0-2)	< 0.001
Ischemic heart disease, count (%)	27 (2.6)	96 (28.4)	< 0.001
Congestive heart failure, count (%)	28 (2.7)	60 (17.8)	< 0.001
Hypertension, count (%)	118 (11.4)	141 (41.7)	< 0.001
Diabetes mellitus	69 (6.6)	62 (18.3)	< 0.001
Anticoagulation therapy	31 (3.0)	65 (19.2)	< 0.001
Psychiatric comorbidity, count (%)	142 (13.7)	39 (11.5)	0.312
Substance abuse, count (%)	172 (16.6)	48 (14.2)	0.302
ISS, median (IQR)	24 (17-27)	25 (17-26)	0.911
Blunt trauma, count (%)	1020 (98.3)	331 (97.9)	0.689
Severe head injury, count (%)	651 (62.7)	216 (63.9)	0.694
Severe thoracic injury, count (%)	400 (38.5)	132 (39.1)	0.865
Severe abdominal injury, count (%)	89 (8.6)	28 (8.3)	0.868
SAP*, median (IQR)	144 (120-164)	150 (120-170)	0.073
SAP* < 90 mm Hg, count (%)	83 (8.0)	32 (9.5)	0.396
ICU admittance, count (%)	602 (58.0)	190 (56.2)	0.565
30-day mortality, count (%)	205 (19.7)	111 (32.8)	< 0.001

*Continuous parameters presented as median with interquartile range (IQR), categorical parameters as n (%). CCI, Charlson Comorbidity Index; ISS, Injury Severity Score; SAP, Systolic Arterial Pressure; ICU, Intensive Care Unit. *On arrival to the trauma unit.*

Of all included patients, 316 (23.0 %) died within 30 days. β-blocker users had a significantly higher crude mortality than non-users, 32.8 % vs. 19.7 % ($p < 0.001$, log-rank test) (Figure 5).

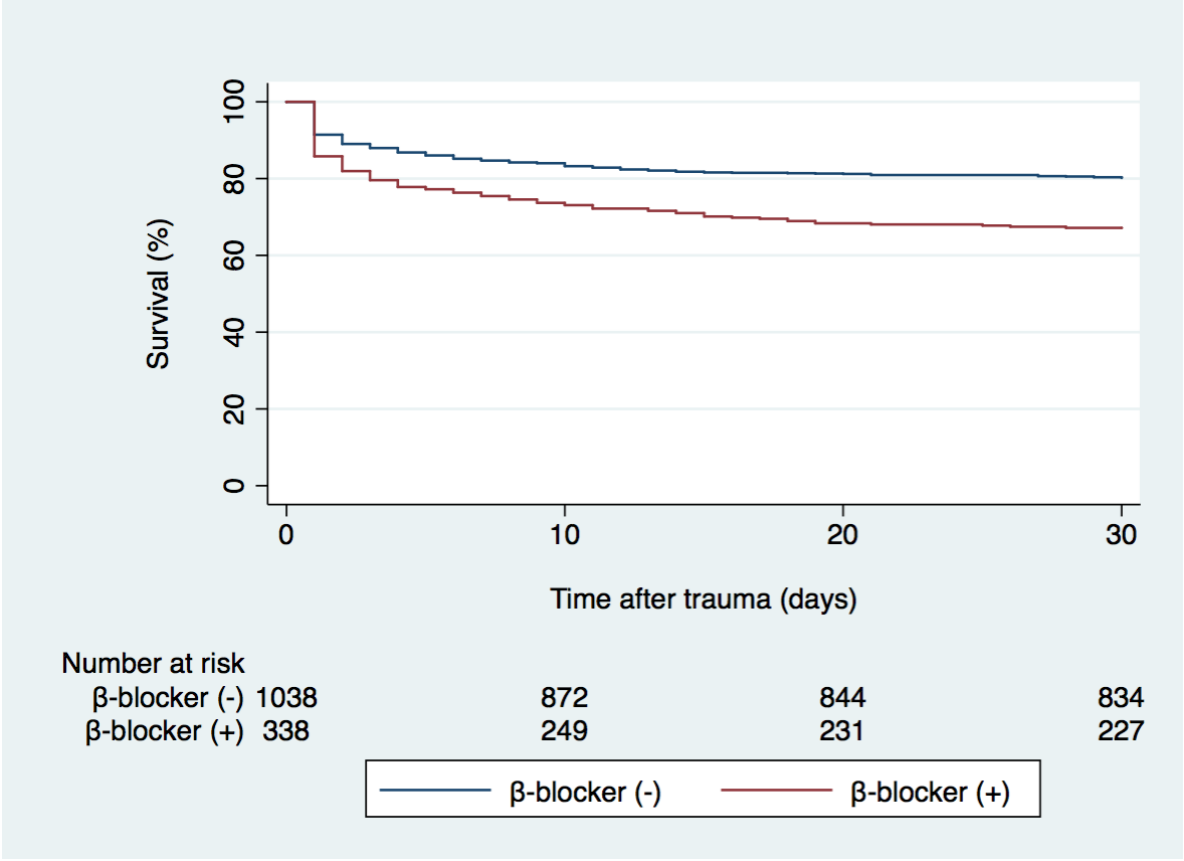


Figure 5. 30-day survival of patients categorized as β-blocker users (β-blocker(+)) or non-users (β-blocker(-)).

In univariate regression analysis, patients treated with β-blockers had increased odds of death, OR 1.99 (95 % CI 1.51-2.61, $p < 0.001$). When adjusted for baseline imbalances and injury-related factors this association was no longer significant, OR 1.09 (0.70-1.70, $p = 0.703$) (Table 5). There were no significant interactions between β-blocker use and head injury or β-blocker use and shock on arrival. When analysed separately, there was no significant association between pre-traumatic β-blockade and mortality for individuals with or without severe head injury respectively.

Table 5. Associations between pre-injury β-blocker use and 30-day mortality, unadjusted and adjusted odds ratio (95 % confidence interval).

	OR (95 % CI)	**p-value**
Unadjusted	1.99 (1.51-2.61)	< 0.001
Restricted model*	1.35 (0.96-1.90)	0.085
Full model**	1.09 (0.70-1.70)	0.703
Full model, missing data analysed with MI***	1.09 (0.73-1.61)	0.675

OR, Odds Ratio; CI, Confidence Interval; MI, Multiple imputations.
** Restricted model: adjusted for age, gender, injury severity, severe head injury and shock on arrival.*
*** Full model: in addition to the restricted model adjusted for education, ischemic heart disease, congestive heart failure, hypertension, diabetes mellitus and anticoagulation therapy.*
**** Full model with multiple imputations of missing data for education.*

5.3 STUDY III

After exclusion of individuals that died before the start of the study period and those with known chronic kidney disease, 413 patients were included in the analysis. The median age in the whole cohort was 40 years, 78 % were male and the vast majority (89 %) presented with blunt trauma. Overall mortality was 8.7 % at 30 days and 11.9 % at one-year post injury. Baseline data for patients with and without AKI are shown in Table 6. 103 patients (24.9 %) developed AKI. KDIGO stages 1, 2 and 3 were noted in 59 %, 13 % and 28 % of AKI patients respectively. 27 patients were treated with continuous renal replacement therapy (CRRT) but none of the survivors were dialysis dependent at three months or one-year follow-up.

Table 6. Baseline characteristics and clinical outcome for patients with and without AKI

	non-AKI	**AKI**	**p**
Count (%)	310 (75.1)	103 (24.9)	
Age, years, median (IQR)	36 (25-51)	54 (36-69)	0.000
Male, count (%)	233 (75.2)	89 (86.4)	0.017
Non-diabetic comorbidity, count (%)	31 (10.0)	24 (23.3)	0.001
Diabetes mellitus, count (%)	9 (2.9)	11 (10.7)	0.001
ISS, score, median (IQR)	24 (17-33)	29 (19-43)	0.000
Blunt trauma, count (%)	273 (88.1)	95 (92.2)	0.239
Admission SAP < 90 mm Hg, count (%)	40 (12.9)	27 (26.2)	0.002
Admission GCS, score, median (IQR)	14 (8-15)	11 (7-15)	0.005
Massive transfusion, count (%)	39 (12.6)	36 (35.0)	0.000
Fluid load 24 hours, L, median (IQR)	5.8 (4.0-8.5)	8.6 (5.3-13.9)	0.005
HES, L, median (IQR)	0.5 (0-1.0)	1.0 (0-1.5)	0.000
HES administered, count (%)	177 (57.1)	74 (71.8)	0.008
Sepsis, count (%)	75 (24.2)	47 (45.6)	0.000
Renal replacement therapy, count (%)	0 (0.0)	27 (26.2)	0.000
ICU length of stay, days, median (IQR)	3.0 (2.0-6.0)	10.0 (4.3-17.0)	0.000
30-day mortality, count (%)	18 (5.8)	18 (17.5)	0.000

Continuous parameters presented as median (interquartile range, IQR), categorical parameters as count and %. ISS, Injury severity score; SAP, systolic arterial pressure; GCS, Glasgow coma scale; HES, hydroxyethyl starch. Admission refers to the admission to the trauma unit.

AKI was significantly associated with increased mortality at 30 days and after one year (Figure 6).

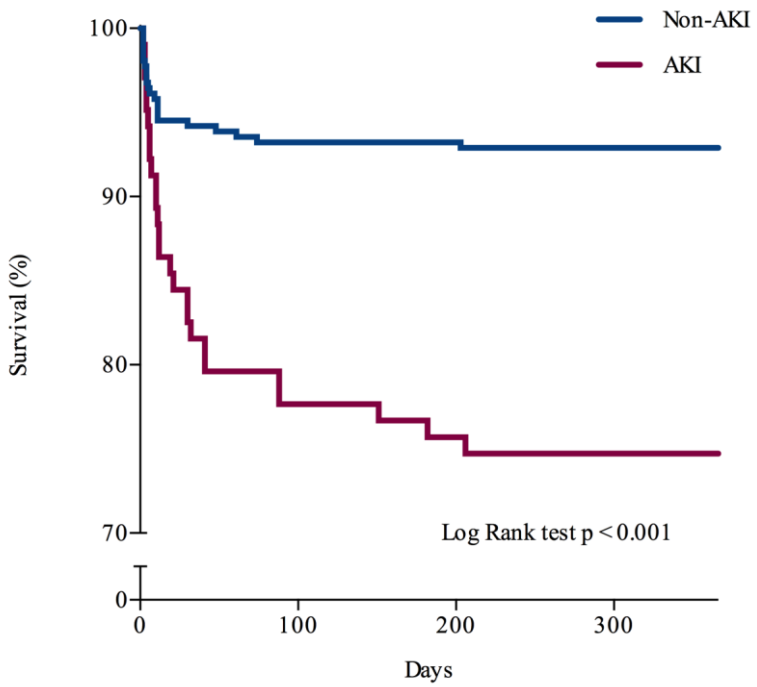


Figure 6. Kaplan-Meier survival curve for one-year post-injury survival for patients with AKI (n = 103, red line) and without AKI (n = 310, blue line).

In univariate logistic regression analysis male gender, age, diabetes mellitus, non-diabetic somatic comorbidity, ISS > 40, massive transfusion, administration of HES, sepsis and shock on arrival (SAP < 90 mmHg on arrival to the trauma unit) were all significantly associated with post-traumatic AKI. In the multivariable model all variables except sepsis and shock remained independent risk factors for AKI (Figure 7).

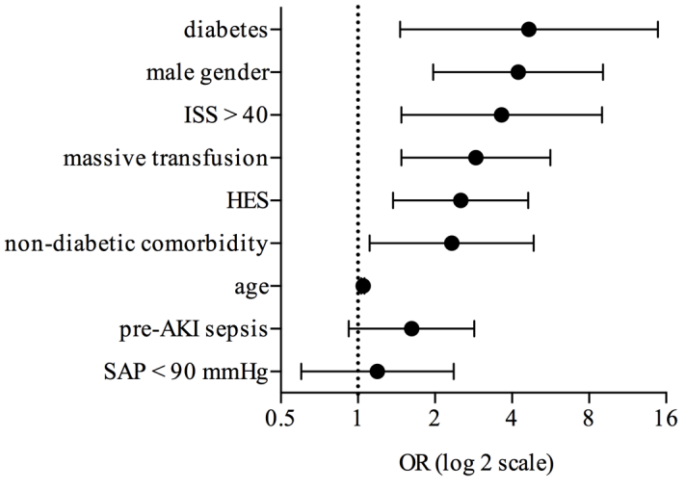


Figure 7. Multivariable associations for AKI risk, odds ratio and 95 % confidence interval. ISS, injury Severity Score; HES, hydroxylethyl starch; AKI, acute kidney injury; SAP, systolic arterial pressure.

5.4 STUDY IV

7382 patients and 36759 matched controls were included, general characteristics are presented in Table 7.

Table 7. General characteristics of the study cohort and control group.

	Trauma patients	**Controls**
n	7382	36759
Gender, n (%)		
Female	2297 (31.1)	11436 (31.1)
Male	5085 (68.9)	25323 (68.9)
Age		
Median (IQR)	39 (25-55)	39 (25-55)
Comorbidity, n (%)	2869 (38.9)	9115 (24.8)
Psychiatric	989 (13.4)	2017 (5.5)
Substance abuse	1029 (13.9)	1053 (2.9)
Somatic	1805 (24.5)	7142 (19.4)
Mechanism of injury, n (%)		
Traffic related	3926 (53.2)	
Fall	2087 (28.3)	
Assault	829 (11.2)	
Self inflicted	267 (3.6)	
Others	271 (3.7)	
Violence, n (%)		
Blunt	6914 (93.7)	
Penetrating	468 (6.3)	
ISS		
Median (IQR)	5 (2-14)	
ISS >15, n (%)	1764 (23.9)	
Mortality, n (%)		
30-days	370 (5.0)	30 (0.1)
1-year	526 (7.1)	317 (0.9)
3-year	662 (9.0)	796 (2.2)
Total follow-up	755 (10.2)	1089 (3.0)

The overall mortality rate was significantly increased over the study period in the trauma cohort compared to the control group (Figure 8).

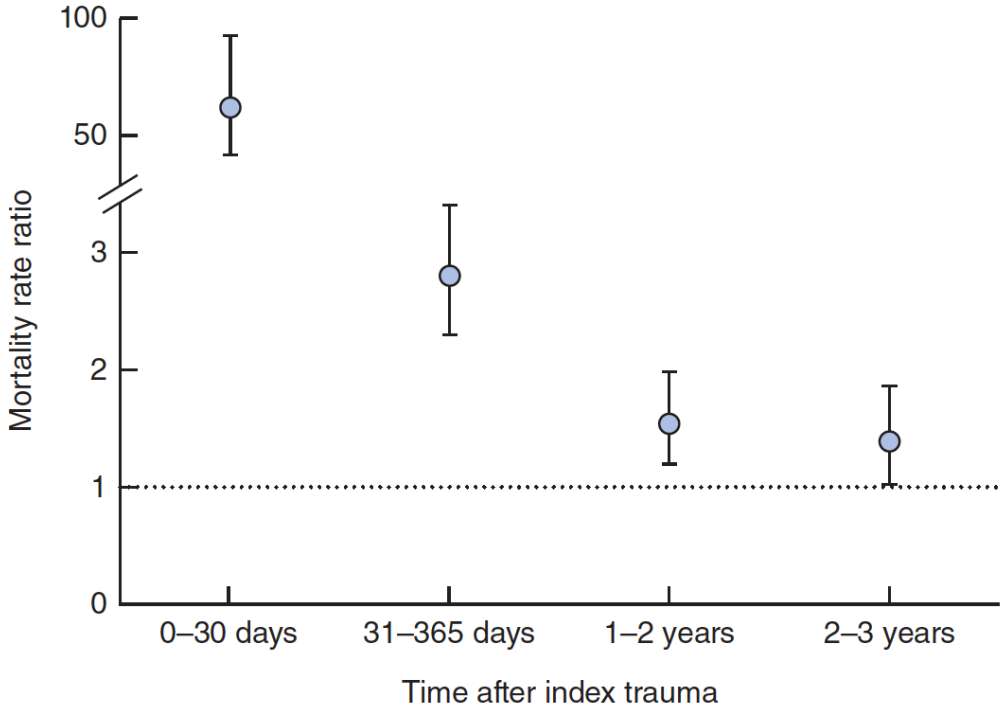
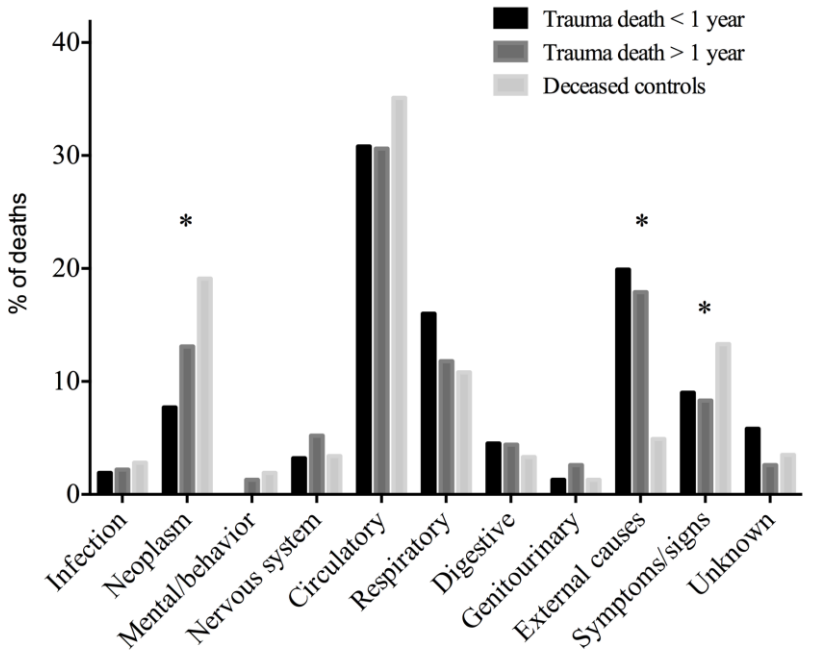
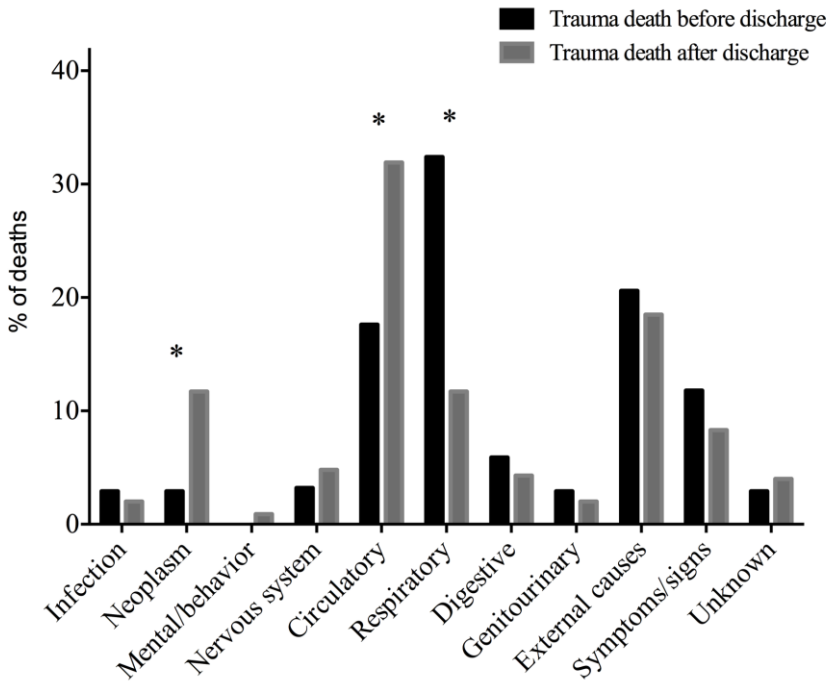


Figure 8. All cause mortality rate ratio with 95 % confidence interval for injured patients versus non-injured controls.

For trauma patients the most common causes of late death were diseases of the circulatory system and external causes. Neoplasms and diseases of the circulatory system were the most frequent causes of death in the control group. Trauma patients were more likely to die from an external cause of death and less likely to die from neoplasms than individuals in the control group (Figure 9a). When comparing late trauma deaths occurring before and after discharge, patients who died while still in hospital were more likely to die from respiratory causes whereas patients deceased after discharge were more likely to die from neoplasms and diseases of the circulatory system (Figure 9b).



a Trauma deaths before and after 1 year versus controls



b Trauma deaths before versus after discharge

Figure 9. Proportions of late death by cause, classified according to ICD-10: **a** for injured patients who died between days 31 and 365 or more than 365 days after index trauma, compared with controls; **b** before and after discharge for injured patients. *P < 0.050 (any difference between all three groups in **a**, versus after discharge in **b**).

There were different distributions of age, comorbidities and injury severity between survivors and non-survivors of trauma. Patients with an external cause of death had a very high prevalence of psychiatric co-morbidity and substance abuse (Table 8).

Table 8. Characteristics of patients who died more than 30 days after the index trauma compared with trauma survivors.

	Non-survivors		Survivors	p
	External cause of death	**Non-external cause of death**		
n	72	313	6627	
Gender, n (%)				
Female	17 (23.6)	95 (30.4)	2070 (31.2)	0.364
Male	55 (76.4)	218 (69.6)	4557 (68.8)	
Age, median (IQR)	52 (36-61)	70 (56-83)	37 (24-51)	< 0.001
Comorbidity, n (%)	53 (73.6)	248 (79.2)	2332 (35.2)	< 0.001
Psychiatric	27 (37.5)	51 (16.3)	858 (12.9)	< 0.001
Substance abuse	31 (43.1)	70 (22.4)	872 (13.2)	< 0.001
Somatic	22 (30.6)	219 (70.0)	1371 (20.7)	< 0.001
ISS				
Median (IQR)	14 (5-25)	10 (5-17)	5 (2-13)	< 0.001
ISS >15, n (%)	35 (48.6)	110 (35.1)	1308 (19.7)	< 0.001

Continuous parameters presented as median with interquartile range (IQR), categorical parameters as n (%). ISS, Injury Severity Score.

Late death due to suicide was almost nine times more common among patients with a self-inflicted trauma than in patients with other mechanisms of injury. In addition, suicide was four times more common among injured patients who were discharged alive compared to matched controls. A detailed analysis of post-discharge death from external causes among the injured patients showed that the majority was due to a new trauma or substance abuse/intoxication, including suicide (Figure 10).

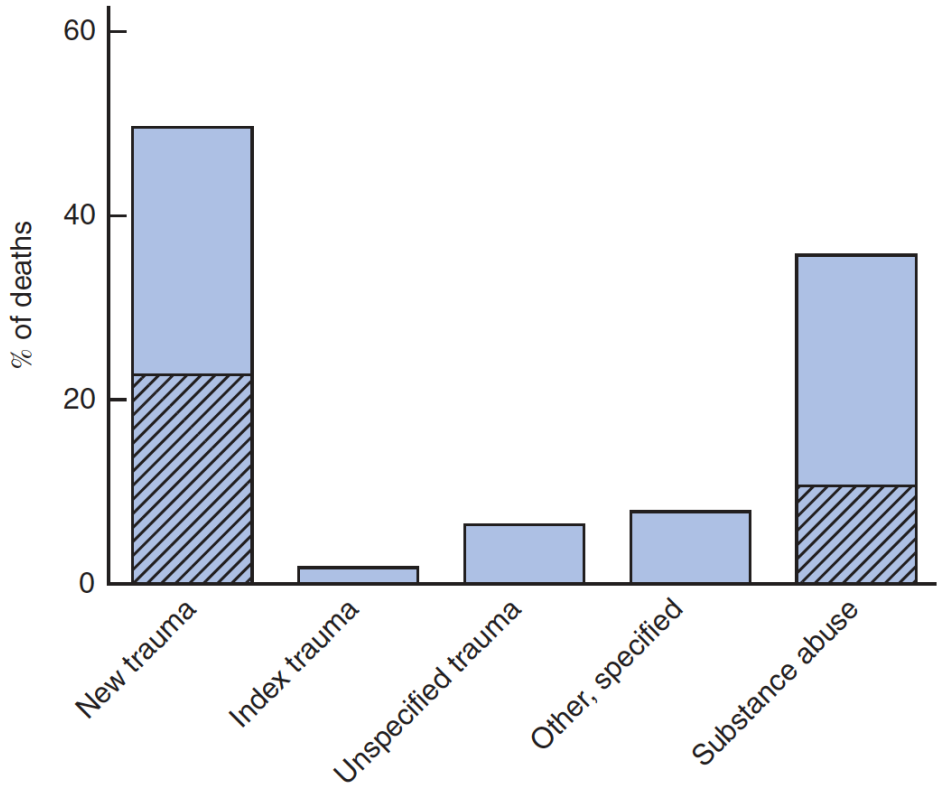


Figure 10. Proportion of late deaths after discharge from external causes according to ICD-10. Hatched shading indicates proportion caused by suicide

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

All included studies in this thesis are observational, epidemiological studies that in general are considered to be of a lower evidence grade than the most common type of experimental clinical study, the randomized controlled trial. However, if well performed observational studies with contemporaneous controls may produce results very similar to results from prospective randomized controlled trials.[110,111] Moreover, some clinical questions could obviously never be answered by prospective randomization due to lack of equipoise or for ethical reasons. The association between pre-traumatic β-blockade and outcome after trauma is one example.

Study I was a case-control study, in general preferred when the outcome of interest is rare.[112] Study II and III were cohort studies with patients extracted from two different local registers, whereas study IV was a matched cohort study with long-term follow up. As previously stated, trauma is a comparatively common cause of death in Sweden. However, admittance with severe injuries to a designated trauma center is a rare outcome from an epidemiologic perspective.

An alternative approach to the case-control design in Study I and the cohort design based on local registers in Study II and IV, would have been to solely use the national registers in Sweden, with traumatic injuries defined from ICD-coding.[113,114] However, patients admitted to trauma centers are different from patients admitted to regular emergency departments, partly due to different mechanisms of injury. There is an accumulation of motor vehicle incidents, assault and high-energy falls and less sports-related injuries and fractures after falls from low levels.[11] Thus, these patients are considered an entity of their own, and using the trauma register enables comparison to other studies within the research field. Moreover, although injury severity can be classified on the basis of ICD-codes, access to extensive original data may have reduced the risk of misclassification of outcome in Study I and provided more precise adjustments for confounders in Study II.

6.1.2 Generalizability

In general, studies are performed to make inferences regarding the population from which the study sample is drawn. The included studies represent the experiences from a single center in northern Europe which of cause may reduce the generalizability and the possibility to draw general conclusions. The Swedish healthcare system, where all trauma patients are treated in the public sector and health care in general is tax-funded, differs from other parts of the world. In addition, the associations between socioeconomic status and trauma risk in study I may be different in countries with lower income or a younger population.

Stating that, the patients included in the studies based on the trauma register (Study I, II and IV) are very similar to other comparable studies regarding baseline characteristics, comorbidity and type of violence.[11,37,38,115]

Inclusion and exclusion criteria in registers and studies are of utmost importance for the ability to extrapolate study results to other contexts; in the trauma setting injury severity is of particular interest. The trauma cohorts in study I and IV were on average moderately injured with a median ISS of 5. Restricting the analyses to the most severely injured did not change the associations significantly, suggesting that our results are generalizable in this aspect.

In Study II, only individuals age 50 or older were included. Thus, we cannot conclude that β-blockade could not be beneficial, or detrimental, among younger individuals. In study III, individuals with a known history of chronic kidney disease were excluded, making inferences on this subgroup impossible. Another aspect is timing of AKI diagnosis, in our material limited from day two to day seven after admission, which may have implications when compared to studies with different timeframes.[70,79]

6.1.3 Misclassification

6.1.3.1 Misclassification of exposure

There are many potential sources of misclassification of exposure in epidemiological research; quality of data, definitions of exposure variables and categorization of continuous variables are among them.

Three of the included studies (I, II and IV) use national registers for ascertainment of exposure and comorbidity classification. The information provided from LISA regarding income and education is considered robust, however, missing data was noted for 9 % of the patients regarding education and 5 % regarding income. The patient register does not include information from primary care and the outpatient part had incomplete coverage during the first years. Thus, we cannot rule out misclassification of individuals with comorbidities of minor severity. The unchanged results regardless of comorbidity definition in Study II, and previous experiences from the research group, suggest that this may be of minor importance.

The definition of users and non-users of β-blockers is essential in Study II. Previous studies suggest that register-based classification of users is valid, especially regarding chronic medications and cardiovascular drugs.[116-120] In support of this is the unchanged result in the sensitivity analysis with different definitions of users. Another aspect is that the majority of deaths after traumatic injuries occur on-stage, or before admittance to trauma centers.[42] If those deceased pre-hospital were more or less likely to use β-blockers is unknown. They were however unlikely to survive regardless of treatment and this is considered a minor problem in Study II but may affect estimates in Study I.

Of particular interest in study III is the definition of sepsis, since sepsis is one of the most important causes of AKI in the ICU-setting. Sepsis has been defined as the combination of

suspected or proved infection *and* physiologic signs of systemic inflammation in response to the infection. Separating injury-related from infectious-related physiologic derangement could be difficult.[121-123] Although efforts have been made to ascertain the presence of infection in the register, we cannot rule out that SIRS in some patients classified as septic was caused by trauma or surgery instead of infection. This might be an explanation to the somewhat unexpected lack of association between sepsis and subsequent AKI.

6.1.3.2 Misclassification of outcome

The Swedish Cause of Death Register has almost 100 % coverage, and death *per se* as an outcome is considered robust. The *underlying* cause of death has been estimated to be approximately 80 % correct.[104] It is considered more accurate among younger individuals and for specific diagnosis, e.g. violent causes of death. In study IV the *immediate* cause of death was used, the validity of this variable is unknown but represents the best possible assessment from the responsible physician. The underlying cause of death is of utmost importance for society and stakeholders and to guide preventive efforts. It is, however, difficult to use in register-based trauma studies since a vast majority of patients will have trauma as the underlying cause of death regardless of clinical course and complications.

The diagnosis of AKI, regardless of definition, is problematic and prone to errors, which may have implications for Study III. The most recent definition, the KDIGO staging, is based on markers of renal function, i.e. glomerular filtration, and not kidney-cell injury. The relative increase in sCr or decrease in urinary output could for example be caused by hypovolemia or, in the trauma setting, under-resuscitation or direct muscle injury without subsequent kidney injury.[80] This issue was addressed by not diagnosing AKI prior to day two. In addition, the biochemical diagnosis of AKI is based on a relative increase in sCr compared to the baseline value, a variable missing in this data set as well as in many others. A common way to address this shortcoming is to impute baseline sCr by back-calculation using the Modification of Diet in Renal Disease (MDRD) equation assuming a low normal glomerular filtration rate of 75 mL/min per 1.73 m^2.[70] This approach might lead to both overestimation and underestimation of AKI, especially of its milder forms.[124]

In study III, baseline sCr was defined as the lower value of the MDRD-imputed sCr or the lowest measured sCr within 24 hours after admission to the hospital. Despite the inherent problems with baseline sCr, a markedly elevated mortality in the AKI-group compared to non-AKI patients was observed, supporting the validity of the AKI classification. Techniques such as MI could be an even better approach to solve this issue.[125]

6.1.4 Confounding

Confounders are by definition factors related to both exposure and outcome, and in opposite to intermediate factors not on the causal pathway between them. Confounders can be handled in the design of the study by randomization, matching or restriction. They can also be addressed in the analysis phase, for example in regression analysis or with stratification.

6.1.4.1 Study 1

The purpose of a control group in a case control study is to estimate the exposure in the population that provides the cases. Matching in case control studies, or any nonrandom sampling, could thus introduce bias since the controls might differ from the entire population from which they were drawn regarding exposure. This was addressed in the analysis phase with conditional logistic regression, keeping the matched groups together. Included patients were also stratified by injury severity.

6.1.4.2 Study II

The study cohort was restricted regarding age and injury severity. Baseline imbalances between β-blocker users and non-users were adjusted for with multiple logistic regression including known and suspected confounders. Missing data was addressed with MI. A propensity score matched data set could have been an alternative but might have produced other problems such as an atypical control group.[126,127]

6.1.4.3 Study III

Patients were restricted regarding presence of chronic kidney disease and survival until day two. Risk factors were analyzed with multiple logistic regression. There were obvious differences in injury severity and associated variables at baseline between the AKI and non-AKI group, which implies that the risk factors associated with AKI should be interpreted with caution in this retrospective study. However, the point estimates for the associations between risk factors and AKI were in general very similar before and after adjustment suggesting that the findings are robust.

6.1.4.4 Study IV

The trauma patients and the control group were matched by age, gender and municipality. Stratified analyses based on injury severity and external causes of death were performed.

Although all studies used methods and models to adjust for measured confounders, the effect of unmeasured confounders could never be ruled out. Moreover, there is little consensus on how to build regression models, which variables to include and which to omit.

6.1.5 Random errors

The results in medical and epidemiological studies are always affected by biologic variation and chance. In general, the study population is a sample from a source population on which we want to make inferences. The magnitude of uncertainty regarding true differences between groups in the source population is reflected by p-values and CI, which will be affected by sample size. The p-value is the probability that the difference between groups found in a study is caused by chance, given the null hypothesis of no difference between these groups in the source population from which we drew our samples. A low p-value indicates that it is very unlikely that a difference as large as the one found is caused by random error only. The CI reflects the interval in which 95 % of our point estimates will be

placed if we resampled new study populations from the source population. Hence, if the 95 % CI for a particular value includes the true value of the source population we do not know.

The large sample sizes in Study I and Study IV reduces the likelihood of random errors. Since the CI for the association between β-blocker use and mortality in study II include 1, we cannot exclude an effect undetected due to lack of power, i.e. a type I error. In Study III, the CIs for several of the included independent variables are wide due to low numbers increasing the uncertainty of these associations. Moreover, the somewhat unexpected finding that there was no increased risk of post-injury AKI despite the occurrence of sepsis might be erroneous, i.e. a type II error.

6.2 INTERPRETATION OF FINDINGS

6.2.1 Risk factors for traumatic events

Socio-economic status is widely considered to be of tremendous importance to general health. A universal definition of socio-economic status, or socio-economic position, is lacking making comparisons between studies and countries difficult. Education and income at an individual level, as used in Study I, are probably the most commonly used proxies but the methodological approach to define them varies.[128] Although the association between a low socio-economic status and the risk of specific injuries has been explored previously, these analyses have not included comorbidities and injury severity in the same analysis. Moreover, there appears to be a gap of knowledge regarding causality; how does differences in socio-economic status translate into increased risk of trauma and poor outcome?[29]

Our results indicate that this association is not fully explained by differences in the prevalence of comorbidities or drug abuse. Several conceptual models have been proposed including different exposure to hazards, different capacities to avoid risk and different opportunities for minimizing physical, psychological and social consequences of injuries.[25] In addition to the increased risk of trauma, individuals with a low socio-economic position have an increased risk of poor physical and physiological outcome if they survive the initial injury.[128]

The risk of experiencing trauma while intoxicated is obvious and needs no further studies. Thus, legal and political actions to reduce the availability of legal and illegal drugs in general and in specific situations such as the traffic is likely to reduce the occurrence of traumatic events. Although the success of preventive efforts could be difficult to appreciate in short term perspective the implementation of evidence-based measures is effective; the reduction of road traffic deaths by 50-75 % in high-income countries and the reduction of child injuries by 80 % in Sweden in the last decades are two examples.[2] The risk of trauma being the greatest with a recent diagnosis of drug abuse points to the particular importance of an active drug abuse, which should alert the clinician caring for these patients.

The association between psychiatric disorders and trauma risk is supported by previous results from population-based studies suggesting an increased risk of accidental death with several mental comorbidities. The increased risk is not fully explained by comorbid substance abuse, and accidental death is more common than suicide among these patients.[129] Our findings, with psychiatric disorders being a significant risk factor after adjustment for drug abuse supports this. The causal link between psychiatric disorders and trauma is thus far from elucidated and goes beyond intoxication and suicide attempts. The deprivation of sleep with several psychiatric disorders, side effects from drugs or relative over-dosing could be contributing to the risk of trauma. Moreover, several psychiatric disorders are associated with risk-taking or self-destructive behavior.[129]

Somatic comorbidity is not only associated with increased risk of trauma, as noted in Study I, but also with increased risk of readmission after discharge, as well as increased short- and long-term mortality after traumatic events.[23,37,38,130] Notably, recent treatment for a somatic disease increased the risk of severe trauma and it could be a marker of more active disease or lower physiologic reserve. Of importance is the identification of the elderly patient with a somatic disorder that makes him or her unfit to drive. The adequate assessment and identification of these individuals is challenging but could reduce the risk of trauma.[131]

6.2.2 β-blockade in the peri-traumatic period

β-blockade has emerged as a potential intervention following severe trauma after the publication of several reports suggesting that post-traumatic administration is associated with reduced mortality and positive outcomes.[132-149] The majority of these studies have focused on TBI, and β-blocker administration has been recommended to victims of severe TBI after hemodynamic stabilization.[150] In addition, the absence of a therapeutic agent that reduces the incidence or severity of MOF together with positive reports from other areas of critical illness has increased the interest in β-blockade within the peri-traumatic period.[59,60]

Several plausible mechanisms for a protective effect of β-blockers in the trauma setting have been presented. A general cardiovascular protective effect is likely in an era of aging trauma patients with a substantial burden of comorbidities.[133,139] This is supported by a lower incidence of myocardial injury noted after post-traumatic administration of atenolol compared to placebo.[132]

Excess catecholamine release and subsequent hyper-metabolism may be harmful as well, especially in TBI, and β-blockade could be protective by attenuating this effect.[151-153] Moreover, β-blockers have complex immunological and hematologic effects not fully understood at the present time, which may be of clinical significance.[137,144,152] Finally, a proposed link between traumatic injuries, elevated levels of catecholamines and endothelial injury resulting in coagulopathy and organ failure have been presented and this chain of events could be a potential therapeutic target.[56]

In study II, patients using β-blockers at the time of trauma had a twofold increase in the odds of death compared to non-users. Thus, at the time of admission, β-blockade use could be seen as a marker of increased risk for poor outcome and as a proxy for frailty that should alert the clinician. After adjustment for trauma-related factors and baseline imbalances, comorbidities in particular, this association was no longer apparent. This indicates that β-blockade *per se* does not increase the risk of death beyond the effects of age, comorbidity and injury severity.

We hypothesized that β-blockade would be protective after adjustment for important confounders but such an effect could not be seen, neither in the full trauma cohort nor in the subgroup with severe TBI. We cannot rule out that there might be such an effect, but it is not likely that further studies using the same methodology could answer this question. Not surprisingly, the users and non-users of β-blockade differed significantly at baseline regarding age and comorbidity. Is it possible to completely adjust for these differences regardless of statistical approach? The OR for the association between β-blockade was strikingly consistent at approximately one, regardless of how the logistic regression was modeled regarding age, comorbidity or injuries. Moreover, the addition of for example ischemic heart disease to the model did not change the OR for the association between β-blocker and death, or the discriminating capacity of the model. This indicates that any unmeasured confounder not included in the study must have an enormous impact to alter the results significantly. One might argue that markers of organ failure instead of 30-day mortality should be used to evaluate a treatment that is supposed to reduce the incidence and severity of MOF. The absence of these data in Study II is a weakness and the inclusion of such parameters could have provided valuable information.

If our observations are valid, why is β-blockade prior to hospitalization protective in general ICU and septic patients but not in the trauma setting?[154-156] A notable difference between these studies and Study II is the lower, or similar, *unadjusted* mortality among β-blocker users compared to non-users, despite a higher prevalence of comorbidities. This suggests a different case mix compared to our material or unmeasured confounders, for example a healthy user effect. In addition, the protective effect may be restricted to those with a cardiovascular reason for admission to the ICU.[154]

Another aspect is the in-hospital continuation versus discontinuation of chronic β-blocker treatment. Studies in patients with acute respiratory failure, heart failure and sepsis have consistently shown a decreased risk of death if β-blocker therapy is continued in-hospital.[157-159] Moreover, the peri-operative continuation of β-blockers in non-cardiac surgery for patients receiving this medication is a Class I recommendation according to European guidelines.[160]

We found no association between β-blockade and shock, and no clinically important difference in blood pressure on arrival between users and non-users in Study II. With the apparent risks associated with discontinuation, our findings may support early reinstitution of β-blockers in the trauma setting in the absence of hemodynamic compromise, although at a low level of evidence.

Regarding post-traumatic administration of β-blockers to patients previously naive to treatment, our data provide no answer. As previously mentioned, this has been recommended in severe TBI with hemodynamic stability.[150] There are some aspects, however, that should be addressed. Firstly, no large prospective RCT with clear allocation has yet been presented. Secondly, individuals exposed to β-blockers in the majority of retrospective studies published had more severe injuries, more complications and a longer length of stay compared to unexposed, but reduced mortality in unadjusted analysis. In addition, the finding that the protective effect of β-blockers is lost in several reports when early deaths are excluded suggests a survival bias.[134,136,140] In conclusion, β-blockers are a rational option in the hypertensive patient after trauma but RCTs are needed before we can recommend it to other groups of patients outside clinical studies.

6.2.3 Acute kidney injury

AKI in patients treated in the ICU is a strong marker of disease severity and consistently associated with increased risk of death. Although hemorrhagic shock and hypoperfusion may cause direct ischemic lesions to the kidney, the pathophysiology of post-traumatic AKI is complex and not fully understood.[161] Obviously, there are patient-related risk factors that we are unable to address; in Study III male gender, age, diabetes and other important comorbidities were all significantly associated with subsequent AKI. These entities, which are in line with previous reports, characterize a high-risk patient in need of special attention.[70,71,162]

Unfortunately, few interventions targeted at preventing AKI in high-risk ICU-patients have been proven successful in clinical trials.[163] In sepsis, a higher compared to a lower blood pressure target reduced the need for renal replacement therapy in patients with chronic hypertension.[164] This effect, however, was not associated with reduced mortality and the strategy was associated with an increased incidence of atrial fibrillation. A higher blood pressure target, when bleeding control is achieved, might be of advantage for the trauma patient with chronic hypertension as well.

The strong association between all included markers of injury severity and shock highlights the need for bleeding control, restoration of circulating volume and homeostasis. Although massive transfusion was associated with an increased risk of AKI in Study III this should probably be interpreted as a marker of injury severity beyond that measured in scoring systems. Current evidence and recommendations strongly imply that the bleeding, traumatized patient should be treated with blood and blood products to avoid death by exsanguination.[14,15] Bleeding control and the reversal of shock is likely of benefit regarding AKI risk as well.

Avoiding interventions or treatments that increases the risk of AKI is of as equal importance as preventive measures. Hetastarches are strongly associated with AKI in sepsis and the US Food and Drug Administration have advised not to use HES in critically ill patients.[18,84,85,165] This association has been less clear in elective surgery and HES is still widely used.[166] In

trauma, older HES-solutions (450/0.7) have been associated with increased AKI risk, in particular in blunt trauma.[86,87] Higher, compared to lower, volumes of HES 130/0.4 were not associated with increased risk of AKI in a retrospective study on elderly trauma patients.[167] In addition, a single center prospective RCT showed decreased incidence of AKI in penetrating trauma with the administration of HES 130/0.4 compared to saline.[88] Although clinical recommendations in general should be based on prospective studies, the results from Study III indicate that resuscitation with HES should be avoided in trauma patients. Moreover, a dose-response association was noted with a significantly increased risk of AKI already after the administration of 500 ml HES suggesting that even low doses may be harmful (unpublished data).

Contrast associated AKI (CA-AKI) is a diagnosis of exclusion and the risk may be overestimated.[163,168] Nevertheless, administration of iodinated radio contrast media has been associated with post-traumatic AKI although results are diverging.[72,81,169,170] Since almost 100 % of included patients in study III received contrast media for computed tomography the addition of CA-AKI to the AKI incidence is difficult to evaluate. However, the finding that larger doses of contrast media (defined as more than one standard dose within the first day) did not increase the risk of AKI is reassuring; radiologic examinations and interventions that reduce the possibility of missed injuries and contribute to bleeding control is probably beneficial for the patient as well as for the kidneys.

One quarter of AKI patients were treated with CRRT, none of the survivors however were dialysis dependent by three months or one year. This is in line with previous findings in the trauma setting suggesting a good potential for renal recovery if the patients is discharged alive from the ICU.[171]

6.2.4 Excess late mortality

Clinical experience and a magnitude of literature suggest that the full impact of trauma cannot be measured solely by short-term measurements, e.g. in-hospital or 30-day mortality. Factors such as quality of life, the ability to return to work and long-term mortality have emerged as important topics in trauma research. Previous studies suggest that age, significant comorbidity, injury severity, discharge destination and socio-economic factors all contribute to the risk of late, post-discharge death after trauma.[23,93,94,172] The results from study IV add to this knowledge by showing that there is a significant increase in mortality several years after trauma in a publicly financed health care system such as the Swedish as well. Moreover, the causes of excess late mortality compared to the background population were identified thus providing an opportunity to improve follow-up and care for these patients.

Simplified, two subgroups of deceased patients could be identified; older individuals with a high prevalence of somatic comorbidity dying from cardiovascular disorders and neoplasms, and younger patients with psychiatric disorders and drug abuse dying from a new traumatic event, suicide or intoxication. The finding that the presence of important somatic comorbidities, especially among the elderly, has a profound effect on long-term survival is

not surprising. Trauma could for these individuals be seen as a marker of frailty and disease progression and some of these deaths might be unavoidable and due to age and underlying diseases. It has been shown that each additional chronic comorbidity increases the risk of hospital readmission significantly after traumatic injuries among elderly.[130] Risk assessment and targeted interventions prior to discharge might be beneficial among high-risk elderly patients in general.[173] It is plausible to assume that this may be of value for trauma patients as well, but this has not been elucidated at present time.

RCTs comparing admittance to inpatient rehabilitation facilities versus other forms of post acute-phase care after multiple trauma are lacking.[174] Stating that, well-performed epidemiological studies have suggested that post-traumatic inpatient rehabilitation improves functional status to a significant degree and reduces long-term mortality.[175] In addition, in a large study from the US, patients of all age groups discharged to a skilled nursing facility were more likely to die than those discharged home, whereas patients discharged to rehabilitation were not.[93] Inpatient rehabilitation is expensive and resource demanding but it is probably beneficial for the severely injured. In a health care system with limited resources the challenge is to identify patients that will benefit the most from these interventions.

The high proportion of recurrent trauma and external causes of death in study IV is notable. The concept of trauma recidivism is old but still valid and seems to be consistent in different parts of the world.[176,177] The presence of psychiatric comorbidities and drug abuse is associated with *de novo*-trauma, as noted in Study I, but also overrepresented among those that died from external causes in Study IV. Individuals with these characteristics are a challenge to the health care system and to society alike, and simple solutions and interventions are unlikely to be found.

Although hospitalization caused by injuries has decreased in the 21st century, with fewer admissions after traffic accidents in particular, death caused by assault has increased to historically high levels among young males in Sweden in the last years.[6] Moreover, death due to intoxication with prescribed or illegal drugs have increased which is of particular concern. Data from the US suggest that there is an alarming "opioid epidemic", with opioid analgesics now being responsible for more deaths than suicide and motor vehicle crashes combined.[178] When converted, the total prescription of therapeutic opioids in the US in 2010 where enough to provide every adult citizen with 5 mg of hydrocodone every 6 hours for 45 days. Although prescriptions in Sweden have increased, studies indicate that the "epidemic" noted elsewhere cannot be seen at the present time.[179] Nevertheless, the prescription pattern of opioids among traumatized patients is largely unknown and the potential for health care associated opioid use and misuse in this group of patients warrants caution. In the absence of positive evidence for opioid use in non-malignant pain, long-term treatment after trauma should be avoided. Further studies are needed to elucidate this topic.

The presented results, with the majority of post-traumatic deaths occurring beyond 30 days, highlight the importance of long-term follow-up to fully address trauma mortality. This is

important for further improvement in trauma care, for the ability to compare results and when evaluating interventions and treatment strategies.

7 CONCLUSIONS

Low education, low income, psychiatric- and somatic comorbidities as well as substance abuse are all independently associated with the risk of becoming a trauma victim. Active substance abuse in particular influences trauma risk. This knowledge might be used for injury prevention among risk individuals.

Pre-traumatic treatment with β-blockers appears to have no association *per se* to short-term mortality after adjustment for relevant confounders. The patient using β-blockers should however be seen as a high-risk individual with an increased risk of death due to a high prevalence of significant comorbidity.

AKI is common among intensive care treated patients after severe injury and strongly related to increased short- and long-term mortality. The risk of end-stage renal disease and dialysis dependency seems to be low among survivors. Somatic comorbidities including diabetes together with markers of injury severity are among the non-modifiable risk factors for AKI. The administration of HES seems to be associated with AKI and cannot be justified in the trauma setting at present time.

Individuals admitted with multiple trauma have an increased risk of death for at least three years after injury compared to uninjured controls of the same age and gender. The excess mortality is largely attributed to trauma recidivism, intoxications and suicide. If these insights could be translated into targeted secondary prevention it could improve outcome.

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